REMARKS

The present invention is drawn to penem compounds having a cis configuration, and substituted at the six-position with a 1-hydroxypropyl group. The present compounds thus have a (1'S, 5R, 6R) configuration, which is equivalent to a (5R, 6R, 8S) configuration. The claimed compounds are particularly effective against methicillin-resistant *staphylococcus* aureus (MRSA) as disclosed in the specification in the paragraph bridging pages 2 and 3.

As presently-claimed, in the formula (I), the 2-position substituent R_1 (when not hydrogen) has been restricted to those groups bonded to the 2-position of the penem skeleton via a thio group.

As a preface to the discussion below of the rejections over prior art, Applicants submit that the following background information is highly pertinent.

As further disclosed at pages 2-3 of the specification, analogous compounds containing a 1-hydroxyethyl group as a 6-position substituent have insufficient activities compared with those having a (1'R, 5R, 6S) configuration. Moreover, it is also known that if the steric configuration of the 6-position hydroxyalkyl group is (1'R, 5R, 6S), compounds containing a propyl or a higher alkyl group as the alkyl group are no longer equipped with any substantial activity. Therefore, the art has primarily investigated substitution at the 2-position for the improvement of activities of penem compounds. Thus, against the above background, it was surprising and unexpected that the presently-claimed compounds possessed the asserted activity.

With an object of creating antibiotics having broad spectrum and high antibacterial activities against pathogenic bacteria with acquired resistance to antibiotics led by highly resistant MRSA which has recently been increasing in number, the invention of the present application was completed as a result of determination of correlations between the kinds and steric configurations of 6-position substituents on the penem ring and biological activities.

Specifically, the invention of the present application is concerned with penem antibiotics characterized by a 1'-hydroxypropyl group at the 6-position of the penem ring and a (1'S, 5R, 6R) steric configuration (hereinafter called "cis-penem propyl derivatives").

Concerning penem compounds, those containing a 1'-hydroxyethyl group as a substituent group on the 6-position of the penem ring and having a (1'R, 5R, 6S) steric configuration, in other words, trans-penem ethyl derivatives have heretofore been reported as subject of research work for the conversion of the 2-position substituent group as in the case of other β-lactam antibiotics. The references cited by the Examiner were published generally in the 1980s. As is readily understood from the technical contents of the references, their publications took place around the same time as interest began to focus on trans-penem ethyl derivatives. Lack of subsequent reports on cis-penems is considered to clearly reflect the history that the subject of subsequent research work increasingly shifted to trans-penem ethyl derivatives.

The rejection of Claims 1 and 37-40 under 35 U.S.C. § 102(b) as anticipated by EP 0069373 to Minamida et al, is respectfully traversed. The Examiner asserts that Minamida et al disclose the racemate of the presently claimed compounds. However, a racemate does not anticipate the compound, because the compounds are not claimed in combination with their enantiomer. Nor would it have been obvious to separate the 1'S from the 1'R enantiomer. Nor does it appear that any 1-hydroxypropyl compound substituted at the 6-position were actually synthesized in Minamida et al.

Minamida et al discloses synthesis of several types of cis-penem ethyl derivatives. It however contains neither disclosure nor suggestion about a correlation between a cis configuration and activity. Concerning the 1'-hydroxypropyl group, in particular, this reference contains no indication even about its steric configuration.

Based on the species on page 11, the Examiner asserts, in effect, that the cis form is in the public domain. However, neither disclosure nor suggestion is made at all about a correlation between a cis configuration and activity. The technical disclosure of this reference is nothing more than a mere reference to certain types of compounds, each of which contains a substituted methyl group on the 6-position of the penem ring. This reference does not provide any problem to be solved for the creation of the penem compound according to the invention of the present application (which contains a 1'-hydroxypropyl group on the 6-position of the penem ring, has a (1'R,5R,6R) steric configuration, and contains a substituted thio group at the 2-position of the penem ring), and does not provide even a motive toward the creation of cis-penem propyl derivatives according to the present invention, let alone disclosure of their creation.

Regarding Claims 37-40, Minamida et al neither disclose nor suggest anything about the use of a penem compound according to the present invention (which contains a 1' - hydroxypropyl group on the 6-position of the penem ring and has a (1'S, 5R, 6R) steric configuration). No limitation whatsoever is, therefore, needed on the active ingredient.

For all the above reasons, it is respectfully requested that the rejection over Minamida et al be withdrawn.

The rejection of Claim 37 under 35 U.S.C. § 103(a) as unpatentable over U.S. 4,540,579 to Afonso et al, is respectfully traversed. Afonso et al is no better than the above-discussed prior art, and indeed Afonso et al direct persons skilled in the art to the (5R, 6S, 8R) configuration and 1-hydroxyethyl as the 6-substituent, i.e., trans-penem ethyl derivatives. In column 2, lines 19-27, (1'R,5R,6S) is stated to be a preferable configuration. Applicants recognize that Afonso et al does disclose cis isomers within their broad disclosure, such as at column 2, line 20. However, Afonso et al neither discloses nor suggests anything about a correlation between a cis configuration and activity. Concerning cis-penem propyl

derivatives, in particular, Afonso et al makes no mention about a problem to be solved, to say nothing of means for solving this problem. Afonso et al does not provide any motivation to make the present invention. The statute requires that the subject matter as a whole must be considered. One skilled in the art would not consider Afonso et al in a vacuum, but would bring to the consideration all prior art knowledge in this field. Armed with such knowledge, one skilled in the art would not be led to the presently claimed compounds.

Nor does Afonso et al disclose a compound having the presently-recited R_1 group.

Accordingly, it is respectfully requested that the rejection over Afonso et al be withdrawn.

The rejection of Claims 1, 17-19, 32-34, 37 and 54-56 under 35 U.S.C. § 103(a) over the literature reference "Synthesis of Optically Active Penems" (Girijavallabhan et al) is respectfully traversed. Girijavallabhan et al is deficient for substantially the same reasons as Afonso et al, which reasons are hereby incorporated by reference. While compound (23) of Girijavallabhan et al does have a (1'S, 5R, 6R) configuration, that compound contains a 1-hydroxyethyl group. Compound (14), which is a trans-isomer of Compound (23), has been reported to have been subjected to a clinical test subsequently. Of record is a copy of a report of this test, as discussed in Mendez et al, "High-performance liquid chromatographic methods for the determination of the penems SCH 29482 and FCE 22101 in human serum and urine," *Biomedical Applications*, Journal of Chromatography, **579**, 115-121 (1992). When this report is taken into parallel consideration, Girijavallabhan et al will be understood to indicate that researchers at that time were interested in the 1'-hydroxyethyl group, especially the trans form and also that even the cis form did not attract researchers' interests or repelled researchers' interests, to say nothing of the 1'-hydroxypropyl group.

Accordingly, it is respectfully requested that the rejection over Girijavallabhan et al be withdrawn.

The rejection of Claims 1-20, 32-24, and 37-68 under 35 U.S.C. § 103(a) as unpatentable over JP 4-69387 to Ishiguro et al, is respectfully traversed. Ishiguro et al relates to a process for the preparation of cis-form penems by irradiation with light. The compounds subjected to photoirradiation are trans-penem ethyl derivatives, and Ishiguro et al contains no disclosure or suggestion whatsoever about a correlation between a cis configuration and activity. Moreover, Ishiguro et al does not disclose any problem to be solved by the creation of cis-penem propyl derivatives. Ishiguro et al does not provide any motivation to make the present invention. The relevant disclosure of Ishiguro et al is no more relevant than that of the other prior art references discussed above. Again, there is no direction in Ishiguro et al to make a 1-hydroxypropyl-substituted compound at the 6-position for a (5R, 6R, 8S) penem, and containing a substituted thio group at the 2-position of the penem ring. Accordingly, it is respectfully requested that the rejection over Ishiguro et al be withdrawn.

The rejection of Claims 1-4, 7-19, 32-34, 37-57, 60, 63 and 66-68 under 35 U.S.C. § 103(a) as unpatentable over U.S. 4,742,052 to Sunagawa et al, is respectfully traversed. Again, and as discussed above, Sunagawa et al is no more relevant than the above-described prior art, since the only disclosure of (5R, 6R, 8S) compounds are those substituted at the 6-position with 1-hydroxyethyl. [A cis-penem compound is disclosed as one of isomers of four types of steric configurations in this reference (column 7, lines 42-63) . Of the four types of steric configurations, however, (1'R, 5R, 6R) and (1'R, 5R, 6S) are described as the most preferred configurations (see column 7, lines 61-63). This reference contains no disclosure or suggestion whatsoever about a correlation between a (1'S, 5R,6R) configuration and activity. As a matter of fact, concerning a 1'-hydroxypropyl group, even its stereostructure is not shown.] Moreover, why would one skilled in the art be led to the (5R, 6R, 8S) configuration, when Sunagawa et al disclose that the (5R, 6R, 8R) and (5R, 6S, 8R) configurations are most preferred? Sunagawa et al contains no disclosure or suggestion

whatsoever about a correlation between a (1'S, 5R, 6R) configuration and activity. Namely, Sunagawa et al does not disclose any problem to be solved for the creation of a cis-penem propyl derivative, and does not provide any motivation to make the present invention. Accordingly, it is respectfully requested that the rejection over Sunagawa et al be withdrawn.

The rejection of Claims 37, 66, and 67 under 35 U.S.C. § 103(a) as unpatentable over U.S. 4,272,437 to Menard et al, is respectfully traversed. While Menard et al disclose broadly hydroxy-substituted lower alkyl groups at the 6-position, 1-hydroxyethyl is disclosed as preferred, as is the (1'R, 5R, 6S) and (1'S, 5S, 6R) disclosed as preferred. Clearly, Menard et al directs one skilled in the art away from the presently-claimed compounds. Menard et al is deficient for essentially the same reasons as the above-discussed prior art.

Nor does Menard et al disclose a compound having the presently-recited R_1 group.

Accordingly, it is respectfully requested that the rejection over Menard et al be withdrawn.

The rejection of Claims 1-29, 32, and 37-68 under 35 U.S.C. § 103(a) as unpatentable over U.S. 4,748,162 over Leanza et al, is respectfully traversed. While Leanza et al disclose individually a 1-hydroxypropyl at the 6-position and the 5R, 6R cis isomer, the reference does not disclose the two in combination. Example 4 thereof, relied on by the Examiner, contains a 2-hydroxy-2-propyl group as the 6-substituent, not the presently-required 1-hydroxypropyl group. Moreover, in column 20 wherein relationships between steric configurations and 6-substituents are disclosed, it is only the trans-form compound (lines 13-20) that contains 1-hydroxypropyl as a preferred 6-substituent, and 1-hydroxypropyl is not included in preferred illustrative 6-substituents for cis forms. Leanza et al does not disclose any problem to be solved for the creation of a cis-penem propyl derivative, and does not provide any motivation to make the present invention. For all of the above reasons, it is respectfully requested that the rejection over Leanza et al be withdrawn.

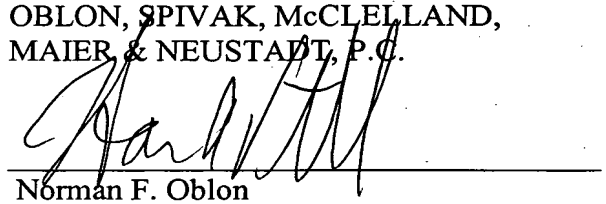
In sum, as we have described above in detail about the individual references, the references contain neither disclosure nor suggestion at all about a correlation between a cis configuration and activity. The cis form cannot therefore be considered to belong in the public domain. The references do not suggest even the structure of a cis-penem propyl derivative, let alone a description of a structure and activity for the creation of the cis-penem propyl derivative. No matter how the references are combined, a motive toward making the present invention, which contains a 1'-hydroxypropyl group on the 6-position of the penem ring, has a (1'S,5R,6R) steric configuration, and contains a substituted thio group at the 2-position of the penem ring, cannot be obtained, to say nothing of a suggestion of the present invention. The present invention is therefore by no means obvious over the references no matter how they are combined.

Regarding the IDS filed July 9, 1999, Applicants note that the English abstracts of the three prior art references submitted therewith also contain information regarding the respective patent families. Each of the three prior art references has at least one corresponding U.S. patent. **Submitted herewith** is a copy of a corresponding U.S. patent for each of the three prior art references, i.e., U.S. 5,191,077; U.S. 5,480,879; and U.S. 5,541,317.

Applicants gratefully acknowledge the examiner's allowance of Claim 35. Nevertheless, Applicants respectfully submit that all of the presently pending claims in this application are in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to Issue.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

Harris A. Pitlick
Registration No. 38,779

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/03)
NFO/HAP/cja